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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,023	06/28/2001	Vladmir R. Muzukantov	PENN-0749	7329

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/762,023	MUZUKANTOV ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *5 and 9*.

   Claim(s) withdrawn from consideration: *NONE*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because:

1. Claim 5 stands rejected under 35 U.S.C. 1 12, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was tiled, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 2/06/04.

Applicant is in possession of a method for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 conjugated t a fibrinolytic or anti-coagulant.

Applicant is not in possession of a method dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising admininstering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds to any "antigen" on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells in claim 5.

Applicant argues that the relationship or correlation between the structure and function of the antibodies as claimed and their function in targeting and delivery of a therapeutic are set forth not only in the definition of non-internalizable antibody at page 9, lines 9-16 of the specification but also in the detailed experiments described for distinguishing internalized antibodies from antibodies not internalized. Applicant asserts that the specification describes the correlation or relationship between the structure of the non-internalizable antibodies and their ability to target and deliver therapeutic agents to the pulmonary vasculature.

However, besides mAB 1A29 antibody, the specification fails to disclose such non-internalizable antibody, the broad brush discussion of making and identifying non-internalizable antibody that binds to any antigen on the luminal surface of the vascular endothelium does not constitute a disclosure of a representative number of members. No such non-internalizable antibodies were made. Only the anti-ICAM-1 monoclonal antibody, mAb 1A29, as non-internalizable antibody, is disclosed. The specification's general discussion of making and identifying for non-internalizable antibodies constitutes an invitation to experiment by trial and error. Such does not constitute an adequat written description for the claimed non-internalizable antibodies.

2. Claim 5 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 conjugated to a fibrinolytic or anti-coagulant; does not reasonably provide enablement for a method dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds to any "antigen" on the luminal surface of the vascula endothelium without subsequent internalization into endothelial cells in claim 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 5/06/04.

Applicant asserts that no reasoning has been provided by the Examiner to establish that a person skilled in the act could not use the genus as whole without undue experimentation. Applicant contends that the previous response provided a publication evidencing the claimed method to be effective with another antibody which binds to an antigen on the luminal surface of the vascular endothelium withou subsequent internalization into endothelial cells. Applicant contends that the phrase "anti-GP85 antibody" was not disclosed in the instant applicantion upon filing does not undermine the teachings of this reference confirming that other antibodies which bind to an antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells, when conjugated to an anti-thrombotic agent, provide effective methods for clot dissolution. Applicant contends that this specific antibody was clearly encompassed with Applicant's broader definition of non-internalizable antibodies and in enabled by the teachings of the instant specification.

Again, Murciano's non-internalizable anti-GP85 antibody, mAb 30B3 was not disclosed in the specification as originally failed. There is insufficient evidence or nexus that would lead the skilled artisan to predict that mAb 30B3 would be non-internalizable antibody and that the ability of anti-GP85 antibody, mAb 30B3, in dissolving intravascular blood clots when conjugated to an anti-thrombotic agent.

3. Claims 5 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowes et (Neurology 1995) of Imaizumi (Transpl. Proc 1994), Mulligan et al (Amer. Pathol. 1993), and Panes (Amer. Physiol. 1995), and further in view of Runge et al and Torchilin et al, and Muzykantov et al (BBA 1986), and Muzykantov et al (Amer J Physiol, 1996) for the same reasons set forth in the previous Office Action mailed 2/06/04.

Applicant argues Mulligan et al do not teach ICAM-1 mAb 1A29 is "not internalized". Applicant's main point is that references relating to anti-ICAM-1 are silent with respect to internalization of the antibody as well as the effects of the conjugating the non-internalizable antibodies with a thrombolytic agent. Applicant concluded that the cited combination of prior art references does not provide the requisite teaching or suggestion to modify their teachings to arrive at the present invention. Applicant contends that these references provide no reasonable expectation that antibodies such as ICAM-1 are not internalized. These references provide no reasonable expectation of success that non-internalized antibodies such as ICAM-1 when conjugated to a fibrinolytic agent would remain bound to the external surface of the pulmonary endothelial cells for a prolonged period of time.

Contrary to applicant assertions the combined teachings of the cited references arrived to the claimed method of dissolving intravascular blood clots in the pulmonary vasculature of an animal with 1A29 mAb conjugated to tPA thrombolytic drug. Given the teachings of Mulligan et al that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, it would be immediately apparent to one skilled in the art that the antibody is non-internalizable.

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc. 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02..

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